

Procalcitonin in Cerebrospinal Fluid as an Important Marker for Diagnosis of Bacterial Meningitis in Children

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ABSTRACT

Background: The aim of this study is to investigate PCT in CSF and evaluate PCT mean values comparing subjects with BM, VM, and other non-infectious diseases. **Methods:** A cross sectional study, conducted to 40 patients, with age range from 3 months to 5 years, 23 child males (57.5%) and 17 child females (42.5%). They were divided into 3 groups; group (1) with BM (20), group (2) with post-neurosurgery (NS) meningitis (8) and group (3) with VM (12). CSF samples were collected as 2 ml CSF from each case, ½ cm for procalcitonin, 1 cm for chemical and microscopical examinations, and ½ cm. procalcitonin levels were determined for each sample. **Results:** There is a high statistically significant difference regarding parameters assessed on CSF analysis among the three studied groups of meningitis, procalcitonin showed a high mean value level among bacterial and post-neuro surgical groups of meningitis compared to viral meningitis. The study shows that the main difference producing high statistically significant difference among three groups was caused by viral meningitis, while the difference between BM and post neuro-surgery was non-significant. Also, there is a statistically significant difference among the three groups of meningitis regarding CSF culture and aspect on analysis. **Conclusion:** CSF procalcitonin is an important marker for early diagnosis of bacterial meningitis and differentiation between bacterial and viral meningitis in order to improve the prognosis of the child disease.

Keywords: Meningitis, Procalcitonin, CSF.

INTRODUCTION

Meningitis is a universal health problem. The laboratory studies play a key role in the diagnosis of the disease and subsequently in the appropriate treatment.^[1]

Procalcitonin (PCT), a protein that consists of 116 amino acids, is considered as a marker of bacterial infections as well as meningitis. It is well known that PCT in healthy subjects is produced by the C cells of the thyroid gland and the neuroectodermal cells of the lungs, nevertheless in negligible levels (0.1 ng/ml). Exposure to bacterial Lipopolysaccharide (LPS) may lead to a 1000- fold increase of PCT in the circulation.^[1,2]

A raised level of PCT in patients with infection has been documented in numerous studies, although the cut-off values have not been established.^[2]

PCT can also increase in stressful conditions such as surgeries, accidents etc. and also tail off and returns to normal-low levels, in 48 to 72 hours. Furthermore, PCT was found to be elevated in the CSF after traumatic brain injury. As compared to control subjects, PCT concentration in CSF was significantly increased in patients with Alzheimer's disease.^[3]

Although the measurement of PCT in serum is now routinely carried out, the significance of PCT in cerebrospinal fluid (CSF) during inflammation or infection is not fully understood.^[4]

A few studies regarding PCT levels in CSF - like ELISA- have presented conflicting results. Several authors have reported the quantitative evaluation of PCT as a diagnostic marker of bacterial meningitis. On the contrary, Gendrel et al.^[5] found that CSF'S PCT in children with bacterial meningitis and viral meningitis was undetectable

In this study, we investigate PCT in CSF and evaluate PCT mean values comparing subjects with bacterial meningitis (BM), viral meningitis (VM), and other non-infectious diseases. So, we aim to detect the level of procalcitonin in children with bacterial meningitis in PICU & other departments as an important marker for diagnosis and proper management.

MATERIALS AND METHODS

A cross sectional study, conducted on 40 patients with meningitis, their age ranged from 3 months to 5 years, they recruited from Intensive Care Unit (ICU), Emergency unit, Internal Medicine, Neurology, and Pediatric departments of El-Hommyat Hospital in Zagazig in the period from January 2017 to November 2017. The 40 patients were divided into three groups: 20 with BM (group 1), 8 with post-neurosurgery (NS) meningitis (group 2), and 12 with

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VM (group 3). They were 23 child males (57.5%) and 17 child females (42.5%), [Table 1].

Ethical considerations: Before the beginning of the study and in accordance with the local regulation followed, the protocol and all corresponding documents were declared for Ethical and Institutional Research Board (IRB) approval in Zagazig University. Also, informed consent was obtained from each child gradians. All patients' data were considered confidential during the study period. This study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: Age group of the patients (3 months – 5 years), both sexes, diagnosed as meningitis or suspected to be CNS infection.

Exclusion criteria: Patient with hospital infections and unavailability of review.

CSF samples were collected from patients by lumbar puncture procedure under complete aseptic condition by needle insertion into the lower back to obtain CSF from inside the spinal cord, as it is the same that paths the brain. We collect 2 ml CSF from each case, ½ cm for procalcitonin, 1 cm for chemical and microscopical examinations, and ½ cm for culture.

Routine investigation includes:

(1) CSF analysis: Aspect, turbid or clear, chemical examination by (Automated autoanalyzer COBAS 6000) for glucose and protein content. Microscopic examination by (Cell count SYSMEX KX 21) for: total leukocytic count, polymorph cells and lymphocytic cells.

Special investigation, procalcitonin level:

In the clinical pathology department, we usually don't analyze CSF procalcitonin as a routine so, we analyze it as a special investigation.

(2) Culture of the collected samples of CSF for differentiation between samples being bacterial, viral or even sterile. CSF samples were collected on Blood and MacConkey agar and incubated at 37 oC for 24 hours.

Colonies were identified by MALDI-TOF (Matrix assisted laser desorption ionization – time of light).

Antibiotic sensitivity for isolated organisms were done by VITEK2

Results were interpreted as regard MIC (Minimal intubation concentration) according to guidelines of CLSI.

Statistical analysis

Measurable investigation was performed utilizing SPSS variant 23.0 programming (SPSS Inc., Chicago, IL, USA). Clear information is abridged as the rate recurrence for all out factors and the mean \pm standard deviation (SD) for ceaseless factors. Consistent factors between two gatherings were investigated utilizing the unpaired Student's t-test or Mann-Whitney U-test, and straight out information were breaking down utilizing the Fisher careful test or chi-squared test, as proper. Contrasts between various gatherings were thought about utilizing single direction investigation of fluctuation with LSD rectification for the least noteworthy distinction. The Pearson coefficient was utilized for relationship investigation. Collector working trademark (ROC) bend examination was utilized to distinguish parameters that were best connected with HF side effects. Ideal cut-off qualities were chosen at the most noteworthy entirety of affectability and explicitness. A two-followed likelihood (p) esteem $<$ 0.05 was considered measurably critical. Intra-and in-between spectator fluctuation was dictated by figuring the coefficients of variety, which were determined as the standard deviations of contrasts between rehashed estimations isolated by the normal estimation of those estimations and communicated as rates.

RESULTS

Table 1: Demographic data of the studied group.

Variables	Studied group (n=40)	
Age/month:	34.28 \pm 16.7 9 months - 5 years	
• Mean \pm SD		
• Range		
Sex	N	%
Male	23	57.5
Female	17	42.5

Table 2: Clinical presentation of the studied group.

Variables	N = 40	%
High fever 39.8 - 41oC	28	70
Low grade fever	10	25
Neck stiffness	14	35
Vomiting, headache and irritability	33	82.5
Coughing	7	17.5
Chest secretions diagnosed as Bronchiolitis	3	7.5
History of complicated parotitis	3	7.5
Severe pneumonia in CXR	2	5
History of ventriculo-peritoneal shunt	8	20

Table 3: CSF analysis among the studied groups of bacterial meningitis

Variables	Group I BM (n=20)	Group II post-NS (n=8)	Group III VM (n=12)	KW* test	p-value
PCT (ng/ml)					
• Mean \pm SD	2.32 \pm 0.698	2.28 \pm 0.78	0.18 \pm 0.24	24.7	0.000**
• Range	1.1- 3.4	1.34 - 3.5	0.05 - 0.75		
Glucose (mg/dl)					
• Mean \pm SD	18.95 \pm 4.8	15.38 \pm 5.28	58 \pm 12.5	24.8	0.000**

• Range	14 - 29	5- 20	28 – 75		
Protein (mg/dl)					
• Mean ± SD	221.5 ± 91.8	259.3 ± 145.5	32.67 ± 19.89	24.7	0.000**
• Range	115 - 409	144 - 474	15 – 70		
TLC (cm2)					
• Mean ± SD	5000 ± 2628.2	4700 ± 3114.5	94.58 ± 37.4	24.7	0.000**
• Range	1000 - 9300	1900-10400	60 – 200		
Polymorph cells (%)					
• Mean ± SD	52.7 ± 19.78	58.4 ± 19.78	4.17 ± 7.93	23.7	0.000**
• Range	5 - 80	40- 80	0 - 20		
Lymphocytes (%)					
• Mean ± SD	60.75 ± 22.3	48.25 ± 22.02	10.0 ± 26.63	18.2	0.000**
• Range	20 - 95	20 - 85	0 - 90		

NS: neurosurgery, *Kruskal Wallis test of non-parametric data, **p <0.001 (highly significant); TLC: total lymphocytic count.

Table 4: LSD within the studied groups in relation CSF analysis.

Variables	Mean difference Group I with	P -value	Mean difference Group II with	p-value
PCT (ng/ml)	Group II=0.046 Group III=2.14	0.857 <0.001	Group III= 2.097	<0.001
Glucose (mg/dl)	Group II=3.58 Group III=38.09	0.292 <0.001	Group III= 42.63	<0.001
Protein (mg/dl)	Group II=37.75 Group III=133.9	0.333 <0.001	Group III= 226.5	<0.001
Total leucocytic count (cm2)	Group II=300 Group III=4905.4	0.759 <0.001	Group III= 4605.5	<0.001
Polymorph cells (%)	Group II=5.68 Group III=48.5	0.401 <0.001	Group III= 54.4	<0.001
Lymphocytes (%)	Group II=12.5 Group III=50.75	0.214 <0.001	Group III= 38.25	<0.001

Table 5: Difference in CSF aspect and culture among the studied groups of meningitis.

Variables	Group I BM (n=20)		Group II post-NS (n=8)		Group III V.M. (n=12)		χ ²	p-value
	N	%	N	%	N	%		
Aspect							40	0.000**
• Clear	0	0.0	0	0.0	12	100		
• Turbid	20	100	8	100	0	0.0		
Culture							37.08	0.000**
• Sterile	15	75	8	100	0	0.0		
• N.M.	2	10	0	0.0	0	0.0		
• Staph.	3	15	0	0.0	2	16.7		
• Viral	0	0.0	0	0.0	10	83.3		

Table 6: Reliability data of PCT as a predictor for early diagnosis of bacterial meningitis.

	AUC	p-value	Sensitivity	Specificity	PPV	NPV	Accuracy
BM	1.0	0.03	94.4%	100%	100%	66.7	95%
Post-NS	1.0	0.04	100	100	100%	100%	100%
VM	0.864	0.247	72.7	100	100	75	83.3%

AUC: area under the curve, PPV: positive predictive value, NPP: Negative predictive value.

Most of the studied cases (82.5 %) complained of vomiting, irritability & headache, 70 % of cases had high grade fever 39.8-41 oC, while there was 7.5% of the cases had history of bronchitis and 5% had sever pneumonia in chest x-ray [Table 2].

In this study, there is a high statistical significant difference regarding parameters assessed on CSF analysis among the three studied groups of meningitis, procalcitonin showed a high mean value level among bacterial and post- neurosurgical groups of meningitis (2.32 ± 0.698 & 2.28 ± 0.78 ng/ml, respectively) compared to viral meningitis (0.18 ± 0.24 ng/ml), [Table 3].

In the present study, 70% of cases had turbid CSF on analysis, more than half of the cases presented with sterile CSF, 12.5% had Staph. bacteria in CSF analysis, 5% had Neisseria meningitidis and 25% had viral infection (fever), [Table 5]. The mean values and range of parameters assessed on CSF analysis, procalcitonin ranged from 0.05 to 3.5 ng/ml among all studied patients with mean value of 1.67 ± 1.18 ng/ml.

We found that the main difference producing statistically highly significant difference among the three groups was caused by group III (viral meningitis), while the difference between group I (bacterial meningitis) and group II (post neuro-

surgery) was non-significant. So, we found a high statistically significant difference among the three studied groups of meningitis regarding CSF culture and aspect on analysis [Table 5].

Regarding the reliability data of PCT as a predictor for early diagnosis of bacterial meningitis shows that the ability of PCT to detect positive cases among true positive was 94.4 %, while, 100 % could exclude negative cases from true negatives with accuracy in diagnosis 95%. Regarding the reliability of PCT to detect positive cases among true positives was 100%, and 100 % could exclude negative cases from true negatives, with accuracy 100% in diagnosis of post neuro-surgical meningitis. Regarding the reliability of PCT as a predictor for early diagnosis of viral meningitis among true positive was 72.7% and 100% could exclude negative cases from true negatives, with accuracy 83,3% in diagnosis of viral meningitis [Table 6].

DISCUSSION

Meningitis is an infection of the membranes (meninges) that cover the brain and spinal cord, which can be due to bacterial, viral and fungal infections. The diagnosis is based on clinical signs and laboratory CSF findings. In the emergency context, direct CSF examination provides evidence of BM (bacterial meningitis) in only 50-80% of cases. It is well known that other methods, which are used for the diagnosis, such as PCR, immunological and biochemical tests have their own limitations. Furthermore, other protein biomarker, such as pancreatic stone protein (PSP), soluble human triggering receptor expressed on myeloid cells 1 (sTREM-1), macrophage migration inhibitory factor (MIF), are not yet established markers of infections.^[6]

At present, only PCT is standardized and used in everyday clinical practice, and despite the big value of PCT, CSF's PCT test is not yet included in daily practices due to its high cost. Procalcitonin is a potentially useful marker in pediatric emergency department. PCT levels in CSF were significantly elevated in the BM group in comparison to VM.

These results are in agreement with other investigations who have evaluated different parameters such as WBS, CRP for the differential diagnosis of BM in patients with a negative direct CSF examination (Gram stain).^[7]

Procalcitonin is an important marker that has been evaluated with regard to its usefulness in distinguishing between the possible causative organism (bacterial or viral) for infections.^[8]

Few published studies have focused on the value of PCT in CSF for the differential diagnosis of BM from VM, which confirmed the association of elevated PCT with bacterial infections.^[9]

The levels of PCT in this study were also correlated with age, something that is in agreement with findings by Singhi et al.^[10] who proposed that high

PCT levels appear to be due to age or age-related disorders of these subjects.

In our study, PCT correlates with duration and severity of infection and has prognostic value for predicting the risk for mortality in critically ill patients with infections and this is with what was approved by Imanda et al.^[11]

In our study also, PCT, apart from a specific marker of bacterial infection, can be considered in deciding which antibiotic is more appropriate to be used.

We assessed also culture of the collected samples of CSF to confirm if the cause of infection is bacterial or viral or even sterile samples by showing the growing organism. This goes in agreement with Jones et al.^[12]

In our study, most of the studied cases (82.5 %) complained of vomiting, irritability and headache, 70 % of cases had high grade fever 39.8 - 41 oC, while there was 7.5% of the cases had history of bronchitis and 5% had sever pneumonia in chest x-ray. This is nearly almost the results belongs to Prat et al.^[13] which stated that cases with vomiting, irritability and headache were about 79.8 %, 75 % of cases had high grade fever 39.5 – 41 oC, 6 % of cases had history of bronchitis and 3.2% had sever pneumonia in chest x-ray.

In our study, 70% of the studied cases had turbid CSF on analysis, more than half of the cases presented with sterile CSF, 12.5% had Staph. bacteria in CSF analysis, 5% had Neisseria meningitidis and 25% had viral infection.

In Grandgirard et al.^[14] result indicating that the commonest causative bacteria presented in the culture of CSF samples were Staph. Aureus and Neisseria meningitidis. The other CSF samples analysis showed Hemophilus influenzae, Streptococcus pneumoniae, Acinetobacter baumannii. The isolated viral species, by real-time PCR, in all subjects with VM were enteroviruses. In our study, the mean values and range of parameters assessed on CSF analysis, procalcitonin ranged from 0.05 - 3.5 ng/ml among all studied patients with mean value of 1.67 ± 1.18 ng/ml.

In our study, there is a high statistically significant difference regarding parameters assessed on CSF analysis among the three studied groups of meningitis, procalcitonin showed a high mean value level among bacterial and post- neurosurgical groups of meningitis (2.32 ± 0.698 and 2.28 ± 0.78 ng/ml, respectively) compared to viral meningitis (0.18 ± 0.24 ng/ml).

This goes in agreement with Wei et al.^[15] which said that the mean value of PCT was significantly higher in patients with BM in comparison to patients with VM (BM: 3.174 ± 1.59 ng/ml, VM: 0.1327 ± 0.03 ng/ml).

In our study, we found that the main difference producing high statistically significant difference among our three groups was caused by group III (viral meningitis), while the difference between

group I (bacterial meningitis) and group II (post neurosurgery) was non-significant. So, we found a high statistically significant difference among the three studied groups of meningitis regarding CSF culture and aspect on analysis.

This goes in agreement with Lacour et al.^[16] which said that there is a high statistically significant difference among BM and VM regarding certain parameters such as leukocytic count ($P < 0.01$), whereas regarding other parameters like glucose, it was significantly decreased ($P < 0.001$) in BM cases. In our study, regarding the reliability data of PCT as a predictor for early diagnosis of bacterial meningitis shows that the ability of PCT to detect positive cases among true positive was 94.4 %, while, 100 % could exclude negative cases from true negatives with accuracy in diagnosis 95%.

This was in agreement with Prat et al.^[13] which referred to the high diagnostic value of PCT test in patients with BM. Its sensitivity was 100%, specificity 96.43%, PPV 95% and NPV 77.14%.

Regarding the reliability of PCT in our study to detect positive cases among true positives was 100%, and 100 % could exclude negative cases from true negatives, with accuracy 100% in diagnosis of post neuro-surgical meningitis. As regard the reliability of PCT as a predictor for early diagnosis of viral meningitis among true positive was 72.7% and 100% could exclude negative cases from true negatives, with accuracy 83,3% in diagnosis of viral meningitis.

Different results by Sedighi et al.^[17] showed that in group with VM, sensitivity was 27.27%, specificity 96.43%, PPV 75%, NPV 77.14%, while our study is 72.7%, 100%, 100%, and 75%, respectively.

Lastly, we want to say that we have a great effort in searching for a similar paper in same aim with ours which approve the great role of the CSF procalcitonin as an important diagnostic marker for early diagnosis of bacterial meningitis and also its great role in differentiation between bacterial and viral meningitis, but, we only found one paper by Gayathri et al.^[18] so this project not discussed adequately, so we try to fulfil part of this project in this study.

Study limitations:

For accurate statistical analysis the sample size must be increased, our sample size is considered too small to perform accurate statistics which considered a limitation in this study. Another limitation of this study was the organisms found is only Strep. Pneumonia we did not find TB meningitis, or fungal for wide coverage of our procalcitonin study. Also, we find only limited papers involving CSF procalcitonin that make the study difficult for discussion and comparison of results.

CONCLUSION

Cerebrospinal fluid procalcitonin is an important marker for early diagnosis of bacterial meningitis and differentiation between bacterial and viral meningitis in order to improve the prognosis of the child disease, as due to their young age, they progress to complications, or even death rapidly.

Recommendations:

1. The sample size must be increased in the future literatures.
2. Future studies in CSF procalcitonin is recommended because there is a lot of studies on serum procalcitonin but very rare CSF calcitonin studies were found.
3. We can decide on the proper treatment with delay or prevention of complications or even death.
4. Culture of the collected CSF samples in order to confirm the cause of meningitis and define the causative organism.

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